REMARKS

Claims 1-7, 9, 12-14, 21-24, 35, 39-41, 44-46 and 51-85 are pending in the subject application. Claim 7 has been canceled herein. Claims 1, 3, 52, 53, 56, 57, 75, 78, 84 and 85 have been amended herein. Support for the amendments is found throughout the specification as filed and no new matter is added by these amendments.

Favorable reconsideration in light of the remarks which follow is respectfully requested.

1. 35 U.S.C. §103 Rejections

Claims 1-7, 9, 12-14, 21-24, 35, 39-41, 44-46, 51, 54, 76 and 83-85 have been rejected under 35 U.S.C. §103(a) as being unpatentable over German Pat. No. 44 47 287 C1 (DE '287) in view of US Pat. No. 5,322,685 (US '685) for the reasons set forth in the previous Office action. In particular, the Office asserted that:

> Applicant's claims are directed toward a topical composition that is able to penetrate the pores even when the pores are smaller than the diameter of the penetrants. The composition is disclosed by applicant as being described in DE '287 (see page 2, first paragraph or applicant's specification). DE '287 refers to the composition as "transfersomes." The transfersomes in DE '287 can contain the antioxidant BHT (see English translation, page 25, second paragraph). The transfersomes can also contain glucocorticoids and mineral corticoids (see page 24 of English translation).

Applicant respectfully traverses this rejection.

Applicants claim, in claim 1, a formulation comprising penetrants being capable of penetrating the pores of a barrier, the average diameter of said pores being smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores. The formulation further comprises at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100% per 6 months. Further, the agent is selected from corticosteroids and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

DE '287 describes preparations for the transport of active substances into and through barriers, such as the skin. The preparations are in the form of liquid droplets suspended in a liquid medium, and are surrounded by a membrane-type sheath of one or several layers of amphiphilic carrier substances with solubilities in the suspension medium differing by a factor of at least 10.

However, DE '287 does not describe a preparation wherein the agent (active substance) is a corticosteroid and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation, as claimed by Applicants. This is acknowledged by the Office in its statement that "The reference (DE '287) does not specifically discuss a formulation that contains the corticosteroids"

Further, Applicants respectfully submit DE '287 does not suggest a preparation wherein the agent (active substance) is a corticosteroid and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation, as claimed by Applicants. DE '287 describes preparations that include at least two different amphiphile components having different solubilities (a more soluble component and a less soluble component). In a limited situation, DE '287 sets out that the active substance can be the **more soluble** component. In this limited situation, it is set out that:

> Where the active substance, for example, Ibuprofin, Diclofenac or a salt thereof is the more soluble component, possibly with the addition of less than 10% by weight related to the total composition of the preparation of another soluble component and wherein the concentration of the more

> soluble component(s) typically amounts to between 0.01% by weight and 15% by weight. (English translation, page 25, lines 4-9)

Thus, according to DE '287, if, and only if, the active agent is the more soluble component, then it can be present in an amount between 0.01% by weight and 15% by weight. However, as previously discussed by Applicant, in no event would the more soluble component be a corticosteroid. Rather, this limited situation applies to certain active substances. In particular, as set out by DE '287, the solubility of the components refers to their solubility in the suspension medium, which is usually water (page 10, lines 5-7). It is well-known that corticosteroids are relatively extended, apolar molecules, which are **not at all soluble** or are, at best, **very poorly soluble** in water (the suspension medium). In no event would a corticosteroid be the more soluble component. As such, the limited situation and the parameters associated with this limited situation would not apply to corticosteroids.

In particular, DE '287 only describes that agents (1) that are soluble in the liquid medium (water) and (2) that are more soluble in the liquid medium (water) than the other ampophilic component can be present in an amount between 0.01% by weight and 15% by weight. This range does not generally relate to active agents, but only to active agents acting as the more soluble component. Corticosteroids will never be the more soluble component and, thus, this range would not apply to corticosteroids. Further, there is no teaching or suggestion that the ranges specified for the more soluble component could apply to anything other than the more soluble component (in this case, a corticosteroid, which would be the less soluble component).

Further, Applicants respectfully disagree with the Office's assertion that even though "The reference (DE '287) does not specifically discuss a formulation that contains the corticosteroids":

> * * *the reference does teach that the amounts of the active ingredients and the carrier substances can be varied to produce a product with the optimum solubility and skin penetration characteristics. Therefore, the reference clearly teaches that the amount of the corticosteroids in the transfersome can be varied in the course of producing the best product possible. Thus, a person of ordinary skill in the art would be motivated to modify the amount of corticosteroid in the transfersome. Such

modification would reasonable lead to the amount of corticosteroid claimed by applicant.

The selection of the suitable amount of agents in a preparation involves a number of factors that must be taken into account. While a particular amount may provide efficiency in delivery, undesirable side effects may be associated with such amounts and, thus, a balance must be reached between providing efficient delivery of an effective dose, while, at the same time, minimizing undesirable side effects. This is not a trivial problem, as is demonstrated by the vast number of formulations on the market for delivery of the same agents. These formulations vary significantly in their composition and, thus, it is demonstrated that "producing the best product possible" will not result in the same end product, or even similar end products with similar components and/or concentrations, due to the large number of possible components and variables which can be taken into account and modified. This lack of a single way of "producing the best product possible" is also demonstrated by the continuing need, to date, for providing improved formulations with better delivery with minimal undesirable side effects.

In particular, in formulating a preparation for the delivery of an agent, it is important to deliver a therapeutically effective amount of agent. However, when delivery is through the pores of the skin, for example, the amount of agent in the preparation that is applied to the skin is not necessarily the amount that is ultimately be delivered through the skin to the delivery site. Thus, the selection of the amount of an agent in a preparation is not a straight-forward task. Administration of corticosteroids in amounts between a few micrograms per square centimeter (for most potent corticosteroid agents) and up to a milligram per square centimeter (for less potent corticosteroid agents) is common. Application below these amounts reduces the ability of the agent to permeate into the skin in a therapeutically acceptable level. Application above these amounts can result in intolerable local, or even systemic, side effects. In particular, raising the concentration of the agent incurs the danger of agent precipitation on the skin and increases the likelihood of side effects. For example, skin irritation is a serious obstacle for successful development and application of a preparation. Still further, the complexity in selecting a suitable amount of agent is

further increased because one must determine whether more systemic or more topical drug action is to be achieved. As set forth above, the required dose of a corticosteroid depends on which specific corticosteroid is being administered. Further, the potential side effects varies for different corticosteroids. For example, more gentle acting agents, like hydrocortisone, only exhibit a rather short and weak activity. The more recently developed agents, such as prednicarbat- or triamcinolone-derivatives, are more potent, act longer, and are more harmful to the body as they can evoke severe side effects if they are applied highly concentrated and/or repeatedly. Therefore, the selection of dosage must be very precise and depends on which type of agent, and further, which particular agent within that group of agents (e.g. which specific corticosteroid) will be used.

The complexity in choosing an agent and concentration is further demonstrated by the enclosed review article by B. Reazzini and N. Pimpinelli, *New and Established Topical Corticosteroids in Dermatology, Clinical Pharmacology and Therapeutic Use,* Am J Clin Dermatol, 2002 (pp. 47-58). As mentioned, in the past, many structural modifications of the respective agents have been made in order to improve the efficacy of topical corticosteroids and to produce drugs with greater potency, which, however, has been associated with an increased likelihood of side effects. For example, betamethasone dipropionate and clobetasol propionate, which are typical examples of potent molecules that can control specific dermatoses very rapidly are, however, associated with a high risk of topical and systemic adverse effects. Thus, the administration of corticosteroids is always connected with undesirable side effects, which are directly related to the efficacy of these drugs. It is clearly described that the modification of corticosteroids for achieving greater potency is often associated with a greater potential for adverse effects (p. 48, par 3). The adverse effects caused by corticosteroids are described (page 51) and are mainly sytemic and topical adverse effects. Topically administered corticosteroids are mostly capable of causing local adverse effects (Table III) such as epidermal atrophy, steroid face, and a number of further partially severe local adverse effects. Dermal changes are characterized by dermal thinning, atrophy and loss of collagen bridges and can be even observed after a few months of local therapy because of collagen's long life. It is further mentioned that

the changes that occur in collagen fibers are also responsible for the widening of blood vessles, etc.

The atrophogenicity of corticosteroids is known to be generally related to their potency. Therefore, attempts to reduce skin atrophy have been made, for example, the combination of topical corticosteroids therapy with a compound such as an anabolic steroid that will stimulate protein synthesis. However, it is further mentioned that, nevertheless, skin atrophy does not regress after discontinuation of corticosteroids.

Again, on page 53, where clinical formulations are described, it is mentioned that the greater the potency, and the greater the therapeutic efficacy, the greater also are the side effects. Further, it is stated that, when a physician chooses a topical corticosteroid for a specific patient, low potency formulations should be used for long term maintenance therapy. The more potent corticosteroids should be used for short periods and at sites such as palms and soled where low potency corticosteroids are ineffective.

Among the presently used compositions mentioned are ointments, creams, lotions, gels and liposomes. It is stated, however, that liposomes are only valuable delivery systems for topical corticosteroids, where a comprised epidermal barrier enables liposomes to penetrate the skin, which clearly shows that the penetration properties of liposimal delivery systems are <u>not</u> at all optimum.

It is further mentioned with respect to the therapeutic use of topical corticosteroids that the adverse side effects can only be controlled by the use of mild, moderately, or highly potent formulations and depends on where the formulation is to be applied, i.e. dependency on the resistance of the respective skin types. Even a weekly pulsed application of topical potent formulation is described in order to reduce the adverse effects induced by the daily application of very potent topical corticosteroids. (p. 55, 2nd par)

Thus, the review article clearly shown that there are severe problems with side effects of corticosteroids. This article suggests several possibilities to optimize the

risk/benefit ratio including: modification of the structure of the active agents, the addition of further ingredients reducing the adverse effects caused by corticosteroids, use of different kinds of formulations which only differ by the use of more or less potent (and, therefore, more or less disadvantageous) agents. It is even suggested that some of the formulations mentioned, namely liposomal formulations, be applied to compromised epidermal barriers as their penetration capability is poor.

Consequently, this article clearly demonstrates that the problems related to the side effects of corticosteroids cannot be solved in a satisfactory manner by present formulations. Therefore, present formulations must be adapted with respect to the potency of the corticosteroid or its amount. Almost all presently approved medicaments containing corticosteroid have corticosteroid contents less than 0.1 weight%. This is because of the adverse effects of corticosteroids, and is exemplified by the attached list of all medicaments containing clobetasol propionate (a potent corticosteroid) presently approved by the FDA. None of these drugs (be it ointment, cream, solution, gel, etc.) contains more than 0.05% of active agent (corticosteroid). The same also applies to other corticosteroid containing drugs which are presently available.

This clearly proves that one of skill in the art would <u>not</u> be motivated to raise the amount of corticosteroid in a transfersome formulation because this would cause severe side effects in all of the known formulation types.

The fact that presently available commercial corticosteroid-based products normally contain the active ingredient in a low percentage range is also due to the fact that, as mentioned above, commercial corticosteroids are practically insoluble in water. This is well known to one of skill in the art. The solubility of corticosteroids, e.g. in pharmaceutically useful oils, is also typically low due to the mismatch between the cholestane backbone of the former and molecular size of the latter. Therefore, corticosteroids tend to form micro-crystals in various formulations unless they are prevented from doing so by use of suitable co-solvents.

Therefore, the use of corticosteroids as active agents in ultradeformable vesicles comprising a mixture of the stable bilayer forming lipid and the bilayer destabilizing amphiphat is not trivial. For practical application, it is necessary to select the largest relative drug amount that, at the same time, does not lead to corticosteroid precipitation and, consequently, to bilayer stiffening and/or clogging of the pores in a semipermeable membrane through which the vesicle should carry the corticosteroid molecules.

Applicants, thus, teach highly adaptable carrier transporting preparations that transport highly potent corticosteroids reliably and at a high degree through the skin, while avoiding undesirable side effects. Applicants further teach preparations that contain a large amount of corticosteroid (above 0.1 weight-%, relative to total dry mass of the formulation) without causing adverse effects on the skin and without compromising the stability and deformability properties of the agent carrier.

DE '287, on the other hand, describes transfersomal compositions. It is mentioned that, among the many agents that may be contained within the transformations, corticosteroids can be included. However, DE '287 does not describe or suggest the use of any particular corticosteroids or amounts of corticosteroids in the compositions. Further, DE '287 does not mention or suggest the many problems with respect to the incorporation of corticosteroids into such compositions, e.g. the side effects of corticosteroids, the solubility of the corticosteroids, the influence of the insolubility of the corticosteroids on the stability of the compositions, etc. Further, DE '287 provides no guidance as to how to select a suitable amount of corticosteroid while addressing these issues. This comes purely from the present invention. As set forth above, these problems with relation to corticosteroids are currently an issue and have not yet been adequately addressed. Thus, "modification" or "variation" of the amounts of corticosteroids in the formulations is not a routine matter which a person of ordinary skill in the art could do nor would modification or variation "reasonably lead to the amount of corticosteroid claimed by applicant."

US '685 does not remedy these deficiencies. US '685 describes a W/O skin cream preparation. Such preparations are not at all comparable with transfersomal

formulations (for the transport of active agents through the skin) in accordance with the present invention. Regardless, US '685 does not teach or suggest Applicants claimed range of above 0.1 weight-% of corticosteroid relative to the dry mass of the formulation. Rather, US '685 specifically teaches use of a well-known amount of 0.05 weight-% (see examples 4 to 7) and not more. Further, US '685 does not provide any motivation for modifying this amount, much less increasing this amount (much less at least doubling this amount) to reach Applicants minimal claimed value. Like DE '287, there is no guidance within US '685 as to how to solve the problems with relation to use of corticosteroids in transfersomal formulations. One of skill in the art would me motivated to utilize less potent corticosteroids or lesser amounts of corticosteroids than those currently used so as to address these problems in view of the various studies (e.g. in light of the review article provided herewith).

Thus, Applicants respectfully submit that claim 1 is patentable over DE '287, alone and in combination with US '685. In particular, neither of these cited references describe or suggest a formulation containing corticosteroids present at a relative content of above 0.1 weight-% in accordance with Applicants' teachings. Rather, DE '287 describes formulations which are optimized to provide optimal penetration of barriers. These formulations are described for use with a wide variety of agents, which may include corticosteroids. However, there is no suggested amount of corticosteroid nor is there any guidance as to how one can go about selecting the amount of corticosteroids in view of the many problems with relation to the use of corticosteroids. US ' 685 is equally deficient. US '685 describes W/O cream preparations, which are very different than the types of formulations described by the present invention and DE '287. US '685 mentions the use of agents, which may include corticosteroids. However, the amounts of corticosteroids suggested by US '685 are half the amount (or less than half) of the presently claimed amounts. Further, there is no suggestion or motivation to modify these values so as to come within Applicants' claimed ranges. Rather, one of skill in the art would be motivated, if anything, to decrease the amount of corticosteroids.

Accordingly, claim 1 is patentable over DE '287 in view of US '685. Claims 2-6, 9, 12-14, 21-24, 35, 39-41, 44-46 and 51-85 depend from claim 1 and, likewise, are patentable over DE '287 in view of US '685.

CONCLUSION

Reconsideration and allowance of claims 1-6, 9, 12-14, 21-24, 35, 39-41, 44-46 and 51-85 is respectfully requested in view of the foregoing discussion. This case is believed to be in condition for immediate allowance. Applicant respectfully requests early consideration and allowance of the subject application.

Applicants believe that no extension of time is required since this response is being filed before the expiration of the specified time period. Applicants, however, conditionally petition for an extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below charge Deposit Account No. **04-1105** for any required fee.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

Lisa Swiszcz Hazzard (Reg. No. 44,368)
EDWARDS & ANGELL, LLP
P.O. Box 55974
Boston, MA 02205
Tel. No. (617) 517-5512

REVIEW ARTICLE

Am J Clin Dermatol 2002; 3 (1): 47-59
1175-0561/02/0001-0047/$25.00/0

New and Established Topical Corticosteroids in Dermatology

Clinical Pharmacology and Therapeutic Use

Benedetta Brazzini and *Nicola Pimpinelli*

Department of Dermatology, University of Florence, Florence, Italy

Contents

Abstract

Currently, topical glucocorticosteroids are the most frequently used drugs in dermatologic practice. Over the years, research has focused on strategies to optimize potency and, in particular, the anti-inflammatory and immunosuppressive capacity of these drugs, while minimizing adverse effects. However, 'ideal' topical corticosteroids have not yet been synthesized. They should be able to permeate the stratum corneum and reach adequate concentrations in the skin without reaching high serum concentrations. Such characteristics can be obtained by increasing the natural lipophilicity of corticosteroids, e.g. by esterification. In the past, many structural modifications have been made to improve the efficacy of topical corticosteroids to produce drugs with greater potency, although this has often been associated with a higher likelihood of adverse effects. Betamethasone dipropionate and clobetasol propionate, known as fifth-generation corticosteroids, are a typical example of potent molecules that can control specific dermatoses very rapidly, but which are associated with a high risk of topical and systemic adverse effects.

Recently, steroid components have been synthesized that aim to have adequate anti-inflammatory effects and minimal adverse effects. The newest topical corticosteroids used for the treatment of different dermatoses and allergic reactions of the respiratory tract (in particular asthma) are budesonide, mometasone furoate, prednicarbate, the di-esters 17,21-hydrocortisone aceponate and hydrocortisone-17-butyrate-21-propionate, methylprednisolone aceponate, alclometasone dipropionate, and carbothioates such as fluticasone propionate. These new topical corticosteroids are evaluated in the current review, which compares the risk/benefit ratio of each molecule with established agents. The new molecules, compared with the well known and established corticosteroids, generally have a higher anti-inflammatory effect, good compliance among patients (only a once-daily application is needed), rarely induce cross-sensitivity reactions and have weak atrophogenicity.

Topical corticosteroids are the most frequently used drugs for the treatment of patients with inflammatory skin diseases. The risks associated with the use of corticosteroids 'parallel' the benefits of therapeutic efficacy, and risk/benefit ratio is related to steroid potency and percutaneous penetration capacity. To understand how a drug's intrinsic activity at the intracellular level is

related to drug delivery from vehicle to site of action, it is necessary to review some pharmacologic principles that characterize the corticosteroid family of molecules.

1. Clinical Pharmacology

1.1 Chemical Structure and Mechanism of Action

Corticosteroids have a basic skeletal structure comprising 17 carbon atoms arranged in four rings: three six-membered and one five-membered. Modifications to this basic steroid structure have led to the development of compounds with varying potencies and adverse effects (figure 1; table I). Cortisone, the first corticosteroid introduced for medical use had no topical activity,[1] but simple reduction of the carbonyl group on position 11 led to the synthesis of hydrocortisone,[2] one of the most commonly used topical corticosteroids. Additional modifications to this molecule, such as the insertion of double bonds and fluoro groups (at position 6 and/or 9), led to the synthesis of more potent drugs characterized by strong mineralocorticoid activity. However, addition of an α-hydroxyl, α-methyl or β-methyl group at position 16 eliminated this problem.

Over the years, research has focused on strategies to optimize the potency and, in particular, the anti-inflammatory and immunosuppressive capacity, while minimizing the adverse effects, of topical corticosteroids. But, 'ideal' topical corticosteroids have not yet been synthesized. They should be able to permeate the stratum corneum and reach adequate concentrations in the epidermis without reaching high serum concentrations. Such characteristics can be obtained by increasing the natural lipophilicity of topical corticosteroids; by esterification, for example. Previously, many structural modifications (such as reduction of the keto group at position 11; hydroxylation or methylation at position 16; removal of the 17α- or 21-hydroxyl group; fluorination at position 6 and/or 9; esterification at positions 16, 17 or 21; insertion of a double bond at position 1 and 2) were made to improve the efficacy of topical corticosteroids. These modifications were performed to produce drugs with greater potency, but were often associated with a greater potential for adverse effects.

Glucocorticosteroids act on different tissues and types of cells at tissue, cellular and intracellular levels. These drugs have specific and nonspecific effects that are related to different mechanisms of action. It is generally believed that most, if not all, the effects of corticosteroids on cells are mediated via the glucocorticoid receptor (GR), a 777 amino acid protein member of the superfamily of ligand-regulated nuclear receptors.[3,4] The GR has a modular structure and its principal functions (transactivation, DNA binding, and ligand binding) are localized to specific domains. The GR is maintained in the cytoplasm as an inactive multiprotein complex of heat shock proteins, immunophilins, cyclophilins and calreticulin. When a steroid hormone binds to its receptor, the complex dissociates and the receptor migrates to the nucleus. Once in the nucleus, the GR binds DNA sequences known as glucocorticoid response elements and provokes up-regulation or down-regulation of responsive genes. The precise molecular mechanism of regulation of gene expression by corticosteroids is still controversial because of the existence of conflicting hypoth eses: the inhibition κB-α up-regulatory model; the protein-protein interaction model; and the competition model.[5] Specific steroid receptors have been demonstrated in normal human epidermis and dermal fibroblasts. The affinities of fibroblasts for corticosteroids are strongly related to the antiproliferative effects of specific steroid molecules.

It is widely accepted that the potent anti-inflammatory and immunomodulatory actions of corticosteroids are due to inhibition of transcription factors, such as activator protein-1 and nuclear factor κB, that are involved in the activation of pro-inflammatory genes. Genes known to be up-regulated by corticosteroids, and which play a role in the resolution of inflammation, include lipocortin 1 and p11/calpactin-binding protein. Both are involved in suppressing the release of arachidonic acid.[5,6] Lipocortin 1 inhibits phospholipase A_2, reducing the amount of arachidonic acid released from phospholipids.[7,8] Corticosteroids also decrease the release of interleukin (IL)-1α, an important pro-inflammatory cytokine,[9] from keratinocytes.

Hence, corticosteroids suppress the production and effects of humoral factors involved in the inflammatory response, inhibit leucocyte migration to sites of inflammation, and interfere with the functions of endothelial cells, granulocytes, mast cells and fibroblasts.[10-13] Corticosteroids reduce eosinophilia in patients with asthma: directly by promoting eosinophil apoptosis; and indirectly by suppressing receptor expression and production of cytokines and growth factors (such as IL-3, IL-5, granulocyte-macrophage colony stimulating factor, and eotaxin) that are involved in eosinophil maturation, recruitment and survival. Corticosteroids also reduce T cell proliferation and increase T cell apoptosis via mechanisms that result, at least partly, from inhibition of the T cell growth factor IL-2.[14] Monocyte apoptosis is increased, and influx of other inflammatory cells is repressed. This is partly due to decreased expression of adhesion molecules, both on migrating cells and target cells, and to reduced expression of cytokines and chemokines from inflammatory sites. Corticosteroids can also deplete the number of Langerhans cells, by cytolysis or by down-regulating the expression of major histocompatibility complex class I.[15]

Table I. Chemical structures of glucocorticosteroids

Chemical name	Derivative of	Structural characteristics
Alclometasone dipropionate	16α-methyl-prednisolone	7α-chloro 16α-methyl 17,21-dipropionate
Beclomethasone dipropionate	16β-methyl-prednisolone	9α-chloro 16β-methyl 17,21-dipropionate
Betamethasone	16β-methyl-prednisolone	9α-fluoro 16β-methyl
sodium phosphate	16β-methyl-prednisolone	21-dihydrogene phosphate
benzoate	16β-methyl-prednisolone	17-benzoate
valerate	16β-methyl-prednisolone	17-valerate
dipropionate	16β-methyl-prednisolone	17,21-dipropionate
Budesonide	16α-hydroxyl-prednisolone	16,17-acetal with butanone
Clobetasol propionate	16α-methyl-prednisolone	9α-fluoro 16β-methyl 17-propionate 21-chloro
Clobetasone butyrate	16β-methyl-cortisone	9α-fluoro 16β-methyl 17-butyrate 21-chloro
Daxamethasone	16α-methyl-prednisolone	9α-fluoro 16α-methyl
acetate	16α-methyl-prednisolone	21-acetate
nicotinate	16α-methyl-prednisolone	21-nicotinate
propionate	16α-methyl-prednisolone	21-propionate
valerate	16α-methyl-prednisolone	21-valerate
sodium phosphate	16α-methyl-prednisolone	21-dihydrogene phosphate
Diflorasone diacetate	16β-methyl-prednisolone	6α-fluoro 9α-fluoro 16β-methyl 17,21-diacetate
Diflucortolone valerate	16α-methyl-$D^{1,2}$-corticosterone	6α-fluoro 9α-fluoro 16α-methyl 21-valerate
Flumethasone pivalate	16α-methyl-prednisolone	6α-fluoro 9α-fluoro 16α-methyl 21-pivalate
Fluocinolone acetonide	16α-hydroxyl-prednisolone	6α-fluoro 9α-fluoro 16,17-acetonide
Fluocinonide	16α-hydroxyl-prednisolone	6α-fluoro 9α-fluoro 16,17-acetonide 21-acetate
Fluticasone propionate	a	a
Halcinonide	16α-methyl-hydrocortisone	9α-fluoro 16,17-acetonide

Continued over page

Table I. Contd

Chemical name	Derivative of	Structural characteristics
Halobetasol propionate	16β-methyl-prednisolone	21-chloro 6α-fluoro 9α-fluoro 16β-methyl 17-propionate
Halomethasone	16α-methyl-prednisolone	21-chloro 2-chloro 6α-fluoro 9α-fluoro 16α-methyl
Hydrocortisone	Hydrocortisone	
sodium phosphate	Hydrocortisone	21-dihydrogene phosphate
sodium succinate	Hydrocortisone	21-succinate
acetate	Hydrocortisone	21-acetate
butyrate	Hydrocortisone	17-butyrate
aceponate	Hydrocortisone	17-propionate 21-acetate
butyrate, propionate	Hydrocortisone	17-butyrate 21-propionate
Methylprednisolone	6α-methyl-prednisolone	6α-methyl-prednisolone
acetate	6α-methyl-prednisolone	21-acetate
sodium succinate	6α-methyl-prednisolone	21-succinate
aceponate	6α-methyl-prednisolone	17-propionate 21-acetate
Mometasone furoate	16α-methyl-prednisolone	9α-fluoro 16α-methyl 17-furoate 21-chloro
Prednisolone	Prednisolone	
sodium phosphate	Prednisolone	21-dihydrogene phosphate
acetate	Prednisolone	21-acetate
valerate, acetate	Prednisolone	17-valerate 21-acetate
Prednicarbate	Prednisolone	17-ethylcarbonate 21-propionate
Prednisone	11-keto-prednisolone	
Triamcinolone	16α-hydroxyl-prednisolone	9α-fluoro 16α-hydroxyl
acetate	16α-hydroxyl-prednisolone	21-acetate
diacetate	16α-hydroxyl-prednisolone	17,21-diacetate
acetonide	16α-hydroxyl-prednisolone	9α-fluoro 16,17-acetonide

a Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)-,S-(fluoromethyl)ester.

Besides the previously mentioned anti-inflammatory and immunosuppressive capacity, topical corticosteroids also have antimitotic and vasoconstrictive effects. Antimitotic effects are secondary to a general reduction of protein synthesis and may explain the therapeutic action of the drugs in scaling dermatoses such as psoriasis.[15,16] The vasoconstrictive properties demonstrated on vascular beds may contribute to the anti-inflammatory activity of topical corticosteroids. However, the mechanism by which corticosteroids induce vasoconstriction is not yet completely clear. It is thought to be related to inhibition of natural vasodilators such as histamine, bradykinins and prostaglandins.[17,18] Regarding the effects of topical cortico-

steroids on human mast cells, clobetasol-17-propionate and fluocinonide decreased histamine content by 85% during 6 weeks of treatment. This suggests that corticosteroids are not immediately harmful to mast cells. Rather, corticosteroids may represent an additional treatment for mast cell-related diseases such as urticaria pigmentosa.[119]

1.2 Adverse Effects

The adverse effects caused by corticosteroids are related mainly to actions on electrolyte and water balance, neoglycogenesis and tissue repair, and to an inhibitory effect on adenohypophyseal function. Most topical corticosteroids are absorbed in quantities that can produce both systemic and topical adverse effects. The principal systemic adverse effects are listed in table II.

The degree of adrenal suppression is related to the potency of each steroid, but also to factors that increase normal penetration of the drug: application on large skin areas, occlusion, inflamed skin, and high concentrations. Clobetasol can induce adrenal suppression, even if applied in small quantities (14 g/week), while optimized betamethasone dipropionate and difluorosone require over 50 g/week to significantly reduce plasma cortisol levels.[120,21] Occasionally, percutaneous absorption of corticosteroids may produce significant metabolic effects. Hyperglycemia and glycosuria have been reported in patients with pre-existing abnormal glucose tolerance after local occlusive therapy with potent corticosteroids.[122] Cushing's syndrome has been reported after topical corticosteroid treatment without occlusion.[123]

However, topical corticosteroids are mostly capable of causing local adverse effects (table III). Epidermal atrophy is expressed by flattening of the Malpighian and horny layers and of the rete

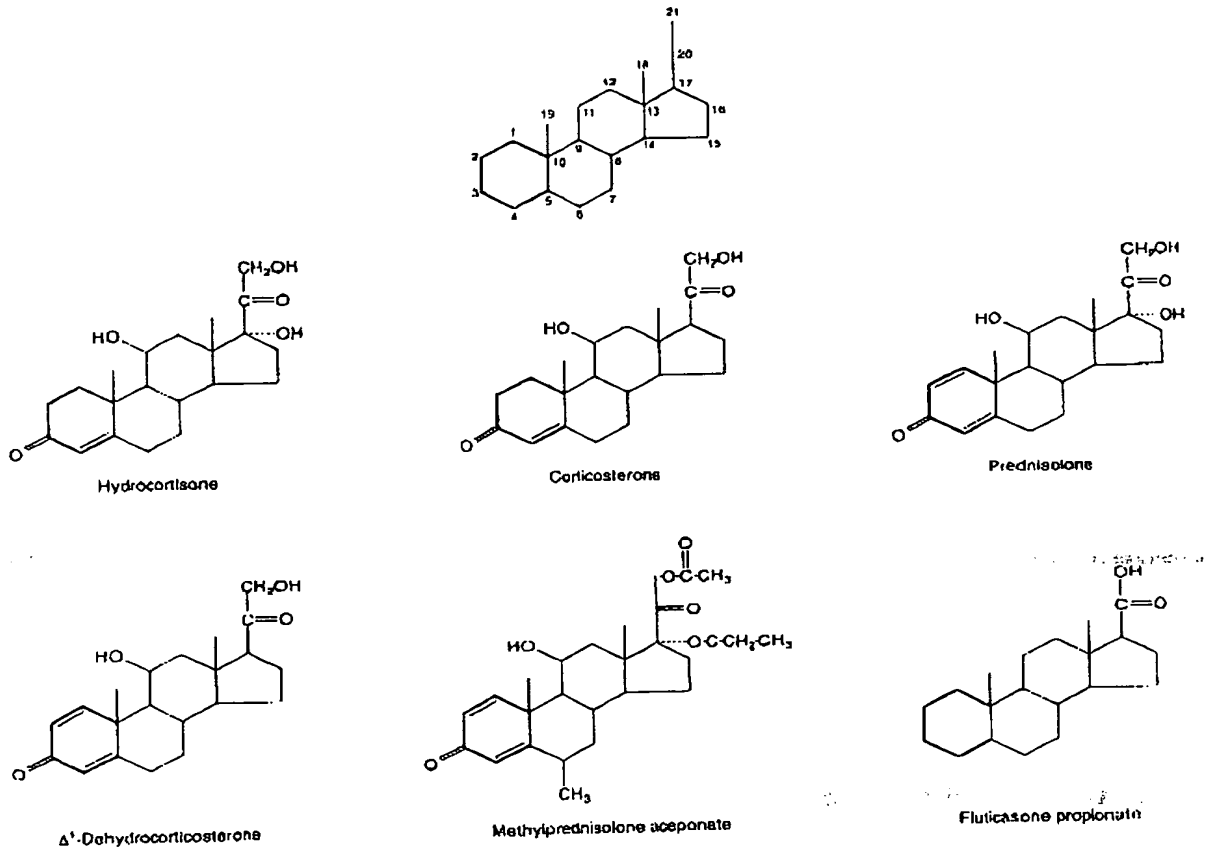

Fig. 1. Basic structure of corticosteroids and new structural modifications.

Table II. Principal systemic adverse effects associated with topical corticosteroids

Bodyweight gain
Cushing's syndrome
Electrolyte imbalance
Hypertension
Diabetes mellitus
Pseudoprimary aldosteronism
Growth retardation
Osteoporosis
Peptic ulcer and gastritis

ridges. Frequently, the size of keratinocytes and of the stratum corneum is decreased, and the amount of melanin transferred to keratinocytes is reduced. Dermal changes are characterized by dermal thinning due to changing viscoelasticity in glycoproteins and proteoglycans responsible for interfibrillar adhesion of collagen. Atrophy and loss of collagen bridges can be observed after a few months of topical therapy, because of collagen's long life. The changes that occur on collagen fibers are also responsible for the widening of blood vessels. Clinically, the skin appears depressed, shiny, wrinkled, very fragile, and often covered with telangiectasia and purpura.[120] The atrophogenicity of corticosteroids is generally related to their potency. Attempts to reduce skin atrophy can be made. For example, it is useful to combine topical corticosteroid therapy with a compound such as an anabolic steroid that will stimulate protein (collagen in particular) synthesis. However, skin atrophy does not regress after discontinuation of corticosteroids.

If corticosteroids are applied for a long period on the face, 'steroid face' may occur. This is characterized by erythema and telangiectasia, or a 'rosacea-like' condition presenting with papules, pustules and telangiectasia on the T area. A pre-existing rosacea can be exacerbated.[125] Besides these two conditions, prolonged use of corticosteroids on the face may lead to the development of papules, pustules, erythema and scaling in the perioral region (perioral dermatitis), especially in women and children.[126] Topical corticosteroids can also induce an acneform eruption or exacerbate a pre-existing acne vulgaris. Corticosteroids probably induce degeneration of the follicular epithelium, causing exit of follicular contents. The acneform eruption is usually characterized by red papules and pustules located around hair follicles of the face, chest and arms. It is important to distinguish this kind of reaction from bacterial folliculitis (*Staphylococcus aureus* and *Propionibacterium acnes*), which usually occurs after occlusion therapy with corticosteroids.[127]

Hypertrichosis is a less common adverse effect that can affect women or children who apply potent topical corticosteroids on the face.[128] The mechanism that leads to hypertrichosis is still unknown. Application of topical corticosteroids for the treatment of eyelid or periorbital dermatoses (seborrhoeic dermatitis, contact and atopic dermatitis, lichen simplex, and blepharitis) is a frequent cause of conjunctival sac contamination, which can lead to glaucoma, ocular hypertension, cataracts, an increased risk of ocular mycotic infections, and exacerbation of Herpes simplex virus infections.[129] Topical corticosteroids are also responsible for masking and exacerbating cutaneous infectious diseases, such as dermatophytic infections ('tinea incognito'),[130] scabies, *Candida albicans* and Herpes simplex infections. Cases of 'eczema craquelé' after potent topical corticosteroid therapy have been described. Most patients underwent occlusive therapy.[131]

Topical corticosteroids have been documented as a frequent cause of true, delayed-type hypersensitivity reactions.[132,133] This concept has been fully realized only in the past 10 years. Non-fluorinated corticosteroids seem to induce contact allergy more easily than fluorinated corticosteroids, probably because the former react, *in vivo*, more rapidly with arginine than fluorinated steroids and may therefore be more likely to induce sensitization.[134,135] In particular, the application of corticosteroids on mucous membranes and skin may induce contact sensitivity that leads to a disseminated or generalized eczematous reaction after local, oral or parenteral exposure.[136] Until now, such clinical manifestations were probably not diagnosed because clinicians were rarely aware of such a possible adverse effect. The prevalence of hypersensitivity to topical corticosteroids has been reported in different studies to be between 0.2 and 5%.[134,135] Patients with allergic contact dermatitis to corticosteroids usually present with a chronic dermatitis that fails to respond to corticosteroids. This nonspecific and self-supporting reaction is very difficult to recognize as iatrogenic because of the clinical manifestations of the steroid's anti-inflammatory effect.

Table III. Principal local adverse effects associated with topical corticosteroids

Skin atrophy
Steroid face
Rosacea
Perioral dermatitis
Corticoid acne
Allergic contact dermatitis
Hypertrichosis
Hypopigmentation
Ocular hypertension
Glaucoma
Cataracts
Worsening of cutaneous infections
Eczema craquelé

Recent studies revealed allergy to several steroid molecules in the same patient, suggesting the possibility of cross-reactions between corticosteroids.[37-39] The existence of cross-reactions was proven by reactions to substances to which the patient had not previously been exposed. Four groups of cross-reacting molecules have been suggested:[39,40]

- **Group A.** Hydrocortisone type: no substitution on the D ring, except a short chain ester on C21, or a thioester on C21; e.g. tixocortol pivalate.
- **Group B.** Triamcinolone acetonide type: C16, C17-cis-ketal or -diol structure.
- **Group C.** Betamethasone type: C16-methyl substitution.
- **Group D.** Hydrocortisone-17-butyrate type: long-chain ester at C17, or C17 and C21 (prednicarbate), with or without C16-methyl substitution.

Clinical observations suggest that tixocortol pivalate can be used as a screening molecule to demonstrate sensitivities to all corticosteroids in group A. Sensitivity to budesonide is a good indicator of subsequent sensitivity to acetonides (group B, to which budesonide actually belongs) and certain esters (group D) such as hydrocortisone-17-butyrate and prednicarbate. However, membership of a certain group does not indicate the sensitizing potential of a given molecule. Some molecules very rarely induce sensitization (betamethasone and its esters, difluocortolone valerate, diflorasone diacetate, clobetasone propionate and butyrate, mometasone furoate, and fluticasone propionate) and can be classified as the less-sensitizing group D corticosteroid esters.

Patients who present with allergic reactions to corticosteroids may have been sensitized to impurities present in commercial formulations or to vehicle systems such as preservatives and bases (lanolin). However, when a patient treated with corticosteroids does not respond, or relapses very quickly, patch tests should be performed to verify sensitivity to the steroid molecule. It is noteworthy that the risk of sensitization to corticosteroids is increased in long term dermatoses.[41] Since most contact allergic reactions to corticosteroids are undiagnosed, in many countries, the standard series has been supplemented with two or three 'screening' corticosteroids: tixocortol pivalate (0.1% petrolatum), budesonide (0.1% petrolatum), and hydrocortisone-17-butyrate (1% ethanol).[42,43]

Long term use of topical corticosteroids may lead to tachyphylaxis (acute tolerance), i.e. the rapidly decreasing response to an active agent after repeated administration of a drug. Tachyphylaxis occurs to the vasoconstrictive and DNA synthesis-suppressing effects of topically applied steroids in hairless mouse skin.[44,45] Unfortunately, tachyphylaxis cannot be avoided by changing the type of steroid applied to the skin within 72 hours of tachyphylaxis being noted.

2. Clinical Formulations

2.1 Potency of Corticosterold Formulations

Topical corticosteroids can be classified according to their relative potency (table IV). The formulations in each group are similar in potency, but not identical. Importantly, the greater the potency, the greater the therapeutic efficacy, but also the greater the adverse effects. When a physician chooses a topical corticosteroid for a specific patient, low potency formulations should be used for long term maintenance therapy. The more potent corticosteroids should be used for short periods and at sites such as palms and soles, where low potency corticosteroids are ineffective.

2.2 Vehicles and Formulations

Besides the steroid active molecule, the potency of each topical formulation can be influenced by vehicle characteristics. Vehicles should allow adequate release of the active compound, should spread easily and be aesthetically pleasant, and should not induce stinging. Some important general rules should be considered when choosing a vehicle:

1. The solubility of the therapeutic agent in the vehicle.
2. The rate of release of the active molecule from the vehicle.
3. The ability of the vehicle to hydrate the stratum corneum and enhance penetration of the active principle.
4. The stability of the steroid molecule in the vehicle.
5. The physical and chemical interactions of the vehicle with the skin and active molecule.
6. The phase of disease.
7. The localization and extent of disease.

The major classes of formulations for corticosteroids are ointments, creams, lotions, and gels. In general, ointments provide good hydration of the stratum corneum, and therefore enhance percutaneous penetration and improve potency. However, ointments are greasy and patients prefer creams, which are cosmetically more acceptable, but provide less hydration of the skin. Regarding the phase of disease, lotions and creams are generally recommended in acute eczema, for example, while ointments are preferred in chronic eczema. Certain areas require the use of specific vehicles to obtain good compliance. Physicians must also remember that when dermatoses have a large extension, good compliance is obtained by prescribing creams and lotions, which are easily applied by patients, rather than ointments. On hairy areas, the best treatment is achieved with lotions or foams. Recently, a new, high-bioavailability foam preparation, with increased efficacy and cosmetic superiority over currently available cream, ointment and lotion formulations, has been approved for marketing in several

Table IV. Relative potency (concentration as % weight/weight) of topical corticosteroid formulations

Corticosteroid	Potency
Class 1 (very potent)	
Clobetasol propionate	0.05
Diflucortolone valerate	0.3
Fluocinolone acetonide	0.2
Halcinonide	0.1
Class 2 (potent)	
Amcinonide	0.1
Betamethasone valerate	0.1
Budesonide	0.025
Desonide	0.05
Desoxymethasone	0.25
Diflorasone diacetate	0.05
Diflucortolone valerate	0.1
Fluclorolone acetonide	0.025
Fluocinolone acetonide	0.025
Fluocinonide	0.05
Fluprednidene acetate	0.1
Flurandrenolone	0.05
Fluticasone propionate	0.05
Halcinonide	0.01
Hydrocortisone butyrate	0.1
Methylprednisolone acoponate	0.1
Mometasone furoate	0.1
Prednicarbate	0.25
Triamcinolone acetonide	0.1
Class 3 (moderately potent)	
Alclometasone dipropionate	0.05
Beclomethasone dipropionate	0.025
Beclomethasone salicylate	0.025
Betamethasone benzoate	0.025
Betamethasone dipropionate	0.05
Betamethasone valerate	0.025 and 0.05
Clobetasone butyrate	0.05
Desoxymethasone	0.05
Flumethasone pivalate	0.02
Fluocinolone acetonide	0.00625 and 0.01
Fluocortolone pivalate	0.2
Flupamerasone	0.3
Flurandrenolone	0.0125
Halometh asone	0.05
Hydrocortisone butyrate	0.1
Hydrocortisone aceponate	0.1
Hydrocortisone valerate	0.2
Triamcinolone acetonide	0.04
Class 4 (mild)	
Dexamethasone	0.01-0.1
Fluocinolone acetonide	0.0025
Fluocortyn butyl ester	0.75
Hydrocortisone (alcohol or acetate)	0.1-1
Methylprednisolone	0.25
Prednisolone	0.5

countries.[46] Also, liposomes can be valuable delivery systems for topical corticosteroids in various dermatologic diseases, but only a compromised epidermal barrier enables liposomes to penetrate the skin. Such formulations are therefore effectively employed in disorders such as eczema, but show no benefit in dermatoses such as psoriasis.[47]

3. Therapeutic Use

3.1 Indications and Guidelines for Topical Corticosteroid Therapy

Topical corticosteroids are recommended for their anti-inflammatory activity in inflammatory skin diseases, but they can also be used for their antimitotic effects and their capacity to decrease the synthesis of connective tissue molecules. Some general rules should be remembered when prescribing topical corticosteroids:[48]

1. Very responsive diseases require mild or moderately potent formulations, while less responsive conditions require high or very high potency corticosteroids sometimes associated with occlusion.
2. Mild formulations should be used on the face, groin, axillae, genital, and perineal areas.
3. Very potent formulations should only be used for short periods (14 to 20 days), or intermittently, to reduce adverse effects and prevent tachyphylaxis.
4. Potent or very potent formulations are usually required on palms and soles, and for lichenified and hypertrophic dermatoses.
5. Occlusion is often needed on palms and soles to enhance penetration of the active molecule through a thicker stratum corneum.
6. Corticosteroids should not be used on ulcerated or atrophic skin.
7. Before starting topical therapy with corticosteroids, verify the absence of underlying infectious diseases.
8. Sudden discontinuation should be avoided, after prolonged use of topical corticosteroids, to prevent rebound phenomena.
9. When treating children, special guidelines should be followed to avoid the disadvantages of under-application or the occurrence of systemic and local adverse effects due to overdosage.[49]
10. Laboratory tests should be performed after long periods of therapy and/or the treatment of large areas.

As an example, atopic dermatitis usually affects children and therefore must be treated with moderately potent formulations: very mild formulations are not suggested because of the high incidence of continuing relapses. Persistent lichenified lesions in adults should be treated short term with potent corticosteroids, which should then be replaced by less potent corticosteroids until

treatment discontinuation. The use of topical corticosteroids on mucous lesions is very useful, but frequently limited by the development of oral or genital candidiasis.

Regarding the frequency of application of topical corticosteroids, Lagos and Maibach[50] concluded, in a recent review of the literature, that once-daily application conferred the same benefits as twice-daily applications. An effective alternative to simple once-daily application is so-called tandem therapy: twice-daily application of the corticosteroid itself and, 12 hours later, of the ointment base alone. In some diseases, such as psoriasis, treated with potent or moderately potent formulations, twice-daily application induced a relatively rapid onset of action. However, reduction of the number of daily applications is important because it decreases the incidence of adverse effects and does not significantly modify the course of healing. In addition, it increases patients' compliance. Adverse effects induced by the daily application of very potent topical corticosteroids (e.g. clobetasol propionate) can be reduced by weekly pulsed application of topical potent formulations. This therapeutic scheme has been used with success in the treatment of various dermatologic disorders, including lymphomatoid papulosis.[51]

Finally, in particularly resistant cases, an occlusive dressing may be useful. Skin occlusion increases steroid penetration about 10-fold, and therefore enhances healing. However, occlusion can lead to sweat retention and infections, and may increase the risk of both local and systemic adverse effects. It is noteworthy that recent reports[52] showed clobetasol-17-propionate lotion under occlusion to induce faster remission of psoriatic lesions than non-occlusive therapy, and relapse and safety characteristics were comparable with the nonocclusive corticosteroid application.

3.2 Risk/Benefit Ratio of New Topical Corticosteroids *vs* Established Corticosteroids

Betamethasone dipropionate and clobetasol propionate, known as fifth-generation corticosteroids, are a typical example of potent molecules that can control specific dermatoses very rapidly, but which are associated with a high risk of both topical and systemic adverse effects. Recently, steroid components have been synthesized that aim to have adequate anti-inflammatory effects and minimal adverse effects. The newest topical corticosteroids used in the treatment of numerous dermatoses and allergic reactions of the respiratory tract (in particular asthma) are budesonide, mometasone furoate, prednicarbate, the di-esters 17,21-hydrocortisone acceponate and hydrocortisone-17-butyrate-21-propionate, methylprednisolone acceponate, alclometasone propionate, and carbothioates such as fluticasone propionate.

Hydrocortisone acceponate, prednicarbate and methylprednisolone acceponate are considered new corticosteroids with significant anti-inflammatory effects, but with the least capacity to induce skin atrophy. Therefore, these three molecules can be used to treat 'difficult' areas such as the face, the scrotum, and large body areas in children, with minimal local and systemic adverse effects.[53] Fluticasone propionate is a fluoromethyl androstane-17β carbiothioate, classified as a potent corticosteroid.[54] In our experience, compared with other potent corticosteroids, fluticasone propionate demonstrated greater anti-inflammatory activity but lower potential to cause adverse effects, both local (e.g. atrophy) and systemic (e.g. adrenal suppression). In addition, hypersensitivity and cross-sensitivity reactions have been reported very rarely.[55,56] In dermatology, fluticasone propionate has proved very suitable for the treatment of atopic dermatitis, psoriasis, intertrigo, nummular eczema, seborrhoeic dermatitis, papular urticaria, etc. Fluticasone propionate offers the advantage of a good response to once-daily application.

Budesonide is a potent, non-fluorinated, topical corticosteroid characterized by lateral chains of butyric acid in position C-16 and C-17. Its potency, according to vasoconstriction tests, ranges between that of betamethasone-17,21-dipropionate and that of clobetasol-17-propionate. Budesonide is responsible for very frequent allergic local reactions when used topically in inflammatory dermatoses.[34,45,57]

Mometasone furoate is a synthetic, 17-heterocyclic steroid that is highly effective as an anti-inflammatory agent, but only half as potent in suppressing the hypothalamic-pituitary-adrenal axis as betamethasone valerate.[58] Mometasone furoate 0.1%, a class 2 (potent) corticosteroid, proved more than twice as effective at reducing ultraviolet B-induced erythema than betamethasone dipropionate 0.05% and betamethasone valerate 0.1%. Compared with betamethasone dipropionate and betamethasone valerate, mometasone furoate has very good compliance among patients since it is applied only once daily. Mometasone furoate induces less skin atrophy than betamethasone dipropionate, it is a highly effective treatment for various corticosteroid-responsive dermatoses (atopic dermatitis, seborrhoeic dermatitis, scalp psoriasis, and psoriasis vulgaris), and it has only limited potential to produce local and systemic adverse effects.[59] Mometasone furoate 0.1%, applied once daily in children with atopic dermatitis, produced greater improvement of the disease than hydrocortisone 1.0% applied twice daily. In addition, children treated with hydrocortisone had suppressed plasma cortisol levels, whereas children treated with mometasone furoate did not.[60]

However, mometasone furoate decreases the synthesis of procollagen peptides for type I and III collagens to the same extent as betamethasone-17-valerate, hydrocortisone and methyl-

prednisolone aceponate.[61] Mometasone furoate is very rarely responsible for hypersensitization and cross-reactions with other topical corticosteroids, and it also has the advantage of once-daily application.[62]

Prednicarbate is a double ester of prednisolone. It seems to be the first topical corticosteroid with an improved risk/benefit ratio, demonstrated both *in vitro* and *in vivo*, when compared with conventional molecules.[63] Prednicarbate has a very high anti-inflammatory capacity, demonstrated by its ability to suppress IL-1α synthesis by keratinocytes. But, it also has limited antiproliferative activity, because it inhibits IL-1α and IL-6 production in fibroblasts to a minor extent when compared with conventional glucocorticosteroids.[64]

Methylprednisolone aceponate is a new, non-halogenated molecule with strong anti-inflammatory activity and weak atrophogenicity. This molecule does not influence the circadian cycle and plasma levels of cortisol. Pharmacologic studies demonstrate that dissociation between topical effects and systemic and local adverse effects has been realized with this molecule.[65-67] In addition, once-daily application is adequate for the treatment of most inflammatory dermatoses, thus contributing to excellent compliance. Methylprednisolone aceponate has been used in many skin diseases, such as atopic dermatitis, seborrheic dermatitis and allergic eczema, with very promising results and with a positive risk/benefit ratio. When compared with hydrocortisone, methylprednisolone aceponate shows similar adverse effects: for example, the extent of the decrease in procollagen peptides in human skin is almost the same;[53] but, methylprednisolone aceponate has much greater vasoconstrictor effects.[68] When compared with mometasone furoate, methylprednisolone aceponate shows equal anti-inflammatory activity, similar cortisol suppression, but fewer local adverse effects.[69] In contrast to fluticasone propionate and mometasone furoate, however, sensitivity to methylprednisolone aceponate has been described and, in particular, this molecule shows cross-reactions with budesonide[57] and hydrocortisone-17-butyrate.[70]

New anti-inflammatory drugs are increasingly being used as topical alternative treatments for inflammatory skin disorders. Pimecrolimus (SDZ-ASM 981), a novel ascomycin macrolactam derivative, recently proved to be an effective topical anti-inflammatory and antipruritic agent in the treatment of atopic dermatitis, psoriasis, and established allergic contact dermatitis to nickel in humans.[71-74] Pimecrolimus is an immunophilin ligand and calcineurin inhibitor that inhibits T cell proliferation and antigen-specific activation. The transcription and release of T helper 1 and T helper 2 cytokines from human type 1 and 2 helper-inducer T lymphocytes are also selectively inhibited. The release of pro-inflammatory mediators from mast cell granules and transcription of the late-phase cytokine tumour necrosis factor-α are suppressed by pimecrolimus.

Besides pimecrolimus, the macrolide lactines, a new class of anti-inflammatories, have attracted special interest regarding minimization of the adverse effects of topical corticosteroids. During the last decade, a member of this class, tacrolimus, proved to be a powerful suppressor of the immune system. Tacrolimus inhibits calcineurin phosphatase and the early expression of genes after T cell stimulation. In particular, there is substantial evidence that tacrolimus interferes with the epidermal cytokine network, T helper 1/T helper 2 balance, co-stimulatory molecule expression (B7-1 (CD80), B7-2 (CD86)), and immunoglobulin E-mediated histamine release from mast cells and basophils. Topical application of tacrolimus is useful in the treatment of patients with pyoderma gangrenosum, lichen planus, alopecia areata and atopic dermatitis, but interestingly, it has not proved effective in psoriasis. Topical tacrolimus is associated with mild local adverse effects (e.g. irritation), but, unlike corticosteroids, it does not cause cutaneous atrophy or contact sensitization.[75-78]

4. Conclusion

The comparison between new and established topical corticosteroids in dermatology stresses the current availability of very useful new molecules, whose main advantage is a clearly improved risk/benefit ratio. This feature is so important that a classification system of topical corticosteroids based on risk/benefit ratio has been previously proposed.[49]

Among these new topical corticosteroids, fluticasone propionate and mometasone furoate show the lowest risk of sensitization, and therefore differ from budesonide and, to a much lesser extent, methylprednisolone aceponate. This latter corticosteroid has the best tolerability in terms of both systemic and local adverse effects. Prednicarbate, a very promising molecule, needs wider evaluation in clinical practice.

References

1. Goldman L, Thomson RG, Trice ER. Cortisone acetate in skin disease: local effect in skin from topical applicants and local injections. AMA Arch Dermatol Syph 1952; 19: 101-2
2. Murray JR. The history of corticosteroids. Acta Derm Venereol 1989; 69 Suppl. 151: 4-6
3. Ballare PL, Baxter JD, Higgins SJ, et al. General presence of glucocorticoid receptors in mammalian tissue. Endocrinology 1974; 94: 998-1002
4. Epstein EH, Bonifas JM. Glucocorticoid receptors of the human epidermis. J Invest Dermatol 1982; 78: 144-6
5. De Bosscher K, Vanden Berghe W, Haegeman G. Mechanism of anti-inflammatory action and of immunosuppression by glucocorticoids: negative interference of activated glucocorticoid receptor with transcription factors. J Neuroimmunol 2000; 109 (1): 16-22
6. Biola A, Pallardy M. Mode of action of glucocorticoids. Presse Med 2000; 29 (4): 215-23

7. Blackwell GJ, Carnuccio R, DiRosa M, et al. Macrocortin: a polypeptide causing the anti phospholipase effect of glucocorticosteroids. Nature 1980; 287: 147-9
8. Hirata F, Schiffmann E, Venkatasubamanian K, et al. A phospholipase A2 inhibitory protein in rabbit neutrophils induced by glucocorticosteroids. Proc Natl Acad Sci USA 1980; 77: 2533-6
9. Kragballe K. Topical corticosteroids: mechanisms of action. Acta Derm Venereol 1989; 69 Suppl. 151: 7-10
10. Prillo JE, Fauci AS. Mechanisms of glucocorticoid action on immune processes. Ann Rev Pharmacol Toxicol 1979; 19: 179-201
11. Vernon-Roberts B. The effects of steroid hormones on macrophage activity Int Rev Cytol 1969; 25: 131-59
12. Thompson J, van Furth R. The effect of glucocorticosteroids on the kinetics of mononuclear phagocytes. J Exp Med 1970; 131: 429-42
13. Newton R. Molecular mechanism of glucocorticoid action: what is important? Thorax 2000; 55: 603-13
14. Ashwell JD, Lu FW, Vacchio MS. Glucocorticoids in T cell development and function. Annu Rev Immunol 2000; 18: 309-45
15. Marks R, Williams K. The action of topical corticosteroids on the epidermal cell cycle. In: Wilson JH, Marks PA, editors. Mechanisms of topical corticosteroid activity. Edinburgh: Churchill Livingstone, 1976; 39-45
16. Munro D, Pringle WM. Psoriasis: its response to dithranol and clobetasol propionate; a comparative study. In: Wilson JH, Marks PA, editors. Mechanisms of topical corticosteroid activity. Edinburgh: Churchill Livingstone, 1976: 88-100
17. Altura BM. Role of glucocorticosteroids in local regulation of blood flow. Am J Physiol 1966; 211: 1393-7
18. Juhlin L, Michaelsson G. Cutaneous vascular reactions to prostaglandins in healthy subjects and in patients with urticaria and atopic dermatitis. Acta Derm Venereol 1969; 49: 251-61
19. Lavker R, Scheckter N. Cutaneous mast cell depletion results from topical corticosteroid usage. J Immunol 1985; 135: 2368-73
20. Scoggins RB, Kliman B. Relative potency of percutaneously absorbed corticosteroids in the suppression of pituitary-adrenal function. J Invest Dermatol 1965; 45: 347-55
21. Ortega E, Burdick KH, Segre EJ. Adrenal suppression by clobetasol propionate. Lancet 1973; 1 (7917): 1200
22. Gomez EL, Frost P. Induction of glycosuria and hyperglycaemia by topical corticosteroid therapy. Arch Dermatol 1976; 112: 1559-62
23. Staughton RCD, August PJ. Cushing's syndrome and pituitary-adrenal suppression due to clobetasol propionate. BMJ 1975; 2: 419-21
24. Fisher DA. Adverse effects of topical corticosteroid use. West J Med 1995; 162: 123-6
25. Litt JZ. Steroid-induced rosacea. Am Fam Phys 1993; 48: 67-71
26. Sneddon IB. Perioral dermatitis. Br J Dermatol 1972; 87: 430-4
27. Hurwitz RN. Steroid acne. J Am Acad Dermatol 1989; 21: 1179-81
28. Rook A, Dawber R. Hypertrichosis. In: Rook A, Dawber R, editors. Diseases of the hair and scalp. London: Blackwell Science, 1982: 256
29. Renfo L, Snow JS. Ocular effects and systemic steroids. Dermatol Clin 1992; 10 Suppl. 3: 505-12
30. Solomon BA, Glass AT, Rabbin PE. Tinea incognita and over-the-counter potent topical corticosteroids. Cutis 1996; 58 Suppl. 4: 295-6
31. Anighogu AN, Maibach HI. Topical corticosteroid therapy. In: Millikan LE, editor. Drug therapy in dermatology. New York: Marcel Dekker Inc., 2000: 1-29
32. English JS. Corticosteroid-induced contact dermatitis: a pragmatic approach. Clin Exp Dermatol 2000; 25 (4): 261-4
33. Baumann L, Kerdel F. Topical glucocorticosteroids. In: Fitzpatrick T, editor. Dermatology in general medicine. 5th ed. New York: McGraw Hill, 1999: 2713-7
34. Thomson KF, Wilkinson SM, Powell S, et al. The prevalence of corticosteroid allergy in two U.K. centres: prescribing implications. Br J Dermatol 1999; 141: 863-6
35. Wilkinson SM, Jones MF. Corticosteroid usage and binding to arginine: determinants of corticosteroid hypersensitivity. Br J Dermatol 1996; 135: 225-30
36. Bircher AJ, Bigliardi P, Zaugg T, et al. Delayed generalized allergic reactions to corticosteroids. Dermatology 2000; 200: 349-51
37. Ohi T. Contact dermatitis due to topical steroids with a conceivable cross-reaction between topical steroid preparations. J Dermatol 1996; 23: 200-8
38. McKenna DB, Murphy GM. Contact allergy to topical corticosteroids and systemic allergy to prednisolone. Contact Dermatitis 1998; 38: 121-2
39. Goossens A, Matura M, Degreef H. Reactions to corticosteroids: some new aspects regarding cross-sensitivity. Cutis 2000; 65: 43-5
40. Coopman S, Degreef H, Dooms-Goossens A. Identification of cross-reaction patterns in allergic contact dermatitis from topical corticosteroids. Br J Dermatol 1989; 121: 27-34
41. Corazza M, Mantovani L, Maranini C, et al. Contact sensitization to corticosteroids: increased risk in long-term dermatoses. Eur J Dermatol 2000; 10 (7): 533-55
42. Drake L, Dinehart S, Farmer E, et al. Guidelines of care for the use of topical glucocorticosteroids. J Am Acad Dermatol 1996; 35 (4): 615-9
43. Isaksson M, Brandao FM, Bruze M, et al. Recommendation to include budesonide and tixocortol pivalate in the European standard series, ESCD and EECDRG: European Society of Contact Dermatitis. Contact Dermatitis 2000; 43 (1): 41-2
44. Du Vivier A, Stoughton RB. Acute tolerance to effects of topical glucocorticosteroids. Br J Dermatol 1976; 94: 25-32
45. Clement M, Phillips H, Du Vivier A. Is steroid tachyphylaxis preventable? Clin Exp Dermatol 1985; 10: 22-9
46. Franz TJ, Parsell DA, Halualani RM, et al. Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. Int J Dermatol 1999; 38: 628-32
47. Schmid MH, Korting HC. Liposomes: a drug carrier system for topical treatment in dermatology. Crit Rev Ther Drug Carrier Syst 1994; 11 (2-3): 97-118
48. Giannotti B, Pimpinelli N. Topical corticosteroids: which drug and when? Drugs 1992; 44 (1): 65-71
49. Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. Br J Dermatol 1998; 138: 293-6
50. Lagos BR, Maibach AI. Frequency of application of topical corticosteroids: an overview. Br J Dermatol 1998; 139: 763-6
51. Paul MA, Krowchuk DP, Hitchcock MG, et al. Lymphomatoid papulosis: successful weekly pulse superpotent topical corticosteroid therapy in three pediatric patients. Pediatr Dermatol 1996; 13 (6): 501-6
52. Van der Vleuten CJ, Van Vlijmen IM, De Jong EM, et al. Clobetasol-17 propionate lotion under hydrocolloid dressing (Duoderm ET) once weekly versus unoccluded clobetasol-17 propionate ointment twice daily in psoriasis; an immunohistochemical study on remission and relapse. Arch Dermatol Res 1999; 291 (7-8): 390-5
53. Mori M, Pimpinelli N, Giannotti B. Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. Drug Saf 1994; 10 (5): 406-12
54. Spencer CM, Wiseman LR. Topical fluticasone propionate: a review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. BioDrugs 1997; 7 (4): 318-34
55. Quintiliani R. Hypersensitivity and adverse reactions associated with the use of newer intranasal corticosteroids for allergic rhinitis. Curr Ther Res Clin Exp 1996; 57: 478-88
56. Wilkinson SM, Beck MH. Fluticasone propionate and mometasone furoate have a low risk of contact sensitisation. Contact Dermatitis 1996; 34: 365-6
57. Corazza M, Virgili A. Allergic contact dermatitis from α-methylprednisolone aceponate and budesonide. Contact Dermatitis 1998; 38: 356-7
58. Goh CL, Lim JT, Leow YH, et al. The therapeutic efficacy of mometasone furoate cream 0.1% applied once daily vs clobetasol propionate cream 0.05% applied twice daily in chronic eczema. Singapore Med J 1999; 40 (5): 341-4
59. Kelly JW, Cains GD, Rallings M, et al. Safety and efficacy of mometasone furoate cream in the treatment of steroid responsive dermatoses. Aust J Dermatol 1991; 32 (2): 85-91

60. Vernon HJ, Lade AT, Weston W. Comparison of mometasone furoate 0.1% cream and hydrocortisone 1.0% cream in the treatment of childhood atopic dermatitis. J Am Acad Dermatol 1991; 24 (4): 603-7
61. Haapasaari KM, Resteli J, Karvonen J, et al. Effect of hydrocortisone, methylprednisolone aceponate and mometasone furoate on collage synthesis in human skin in vivo. Skin Pharmacol 1997; 10 (5-6): 261-4
62. Prakash A, Benfield P. Topical mometasone: a review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. Drugs 1998; 55 (1): 145-63
63. Lange K, Kleuser B, Gysler A, et al. Cutaneous inflammation and proliferation in vitro: differential effects and mode of action of topical glucocorticosteroids. Skin Pharmacol Appl Skin Physiol 2000; 13 (2): 93-103
64. Lange K, Gysler A, Bader M, et al. Prednicarbate versus conventional topical glucocorticosteroids: pharmacodynamic characterization in vitro. Pharm Res 1997; 14 (12): 1744-9
65. Kerekés A, Jahn P, Matthes H, et al. Systemic effects of topically applied methylprednisolone aceponate in healthy volunteers. J Am Acad Dermatol 1993; 28 (5): 789-92
66. Kerekés A, Jahn P, Lange L. Local tolerability of topically applied methylprednisolone aceponate. J Am Acad Dermatol 1993; 28 (5): 786-8
67. Günther C, Kerekes A, Staks T, et al. Percutaneous absorption of methylprednisolone aceponate following topical application of Advantan® lotion on intact, inflamed and stripped skin of male volunteers. Skin Pharmacol Appl Skin Physiol 1998; 11: 35-42
68. Haffmann K, Auer T, Stucker M, et al. Comparison of skin atrophy and vasoconstriction due to mometasone furoate, methylprednisolone and hydrocortisone. J Eur Acad Dermatol Venereol 1998; 10 (2): 137-42
69. Kerekés A, Heger-Mahn D, Kuhlmann RK, et al. Comparison of the local and systemic side effects of methylprednisolone aceponate and mometasone furoate applied as ointments with equal anti-inflammatory activity. J Am Acad Dermatol 1993; 29 (4): 576-80
70. Balato N, Patrone C, Lembo G, et al. Contact sensitisation to 6alpha-methylprednisolone aceponate. Am J Contact Dermat 1997; 8 (1): 24-5
71. Meingassner JG, Grassberger M, Fuhrgruber H, et al. A novel anti-inflammatory drug, Pimecrolimus (SDZ-ASM-981), for the topical and oral treatment of skin diseases: in vivo pharmacology. Br J Dermatol 1997; 137: 568-76
72. Van Leent EJM, Gräber M, Thurston M, et al. Effectiveness of the ascomycin macrolatum SDZ ASM 981 in the topical treatment of atopic dermatitis. Arch Dermatol 1998; 134: 805-9
73. Grossberger M, Baumruker T, Hiestand P, et al. A novel anti-inflammatory drug, SDZ ASM 981, for the treatment of skin diseases: in vitro pharmacology. Br J Dermatol 1999; 141: 264-73
74. Neckermann G, Bavandi A, Meingassner JG. Atopic dermatitis like symptoms in hypomagnesaemic hairless rats are prevented and inhibited by systemic or topical SDZ ASM 981. Br J Dermatol 2000; 142: 669-79
75. Ruzicka T, Assmann T, Homey B. Tacrolimus: the drug of the turn of the millennium? Arch Dermatol 1999; 135: 574-80
76. Assmann T, Homey B, Ruzicka T. Applications of tacrolimus for the treatment of skin disorders. Immunopharmacology 2000; 47 (2-3): 203-13
77. Leung DYM, Suter NA. Cellular and immunologic mechanisms in atopic dermatitis. J Am Acad Dermatol 2001; 44 Suppl. 1: S1-12
78. Bekersky I, Fitzsimmons W, Tanase A, et al. Nonclinical and early clinical development of tacrolimus ointment for the treatment of atopic dermatitis. J Am Acad Dermatol 2001; 44 Suppl. 1: S17-27

Correspondence and offprints: Dr *Nicola Pimpinelli*, Department of Dermatology, University of Florence, Via degli Alfani 37, 50121-Florence, Italy. E-mail: pimpi@ngi.it

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Search Results for 'clobetasol'

Products listed on this page may not be equivalent to one another.

Click on a drug name for more information:

Drug Name	Active Ingredients
CLOBETASOL PROPIONATE	**CLOBETASOL** PROPIONATE
CLOBETASOL PROPIONATE (EMOLLIENT)	**CLOBETASOL** PROPIONATE
CLOBEX	**CLOBETASOL** PROPIONATE
CORMAX	**CLOBETASOL** PROPIONATE
EMBELINE	**CLOBETASOL** PROPIONATE
EMBELINE E	**CLOBETASOL** PROPIONATE
OLUX FOAM	**CLOBETASOL** PROPIONATE
TEMOVATE	**CLOBETASOL** PROPIONATE
TEMOVATE E	**CLOBETASOL** PROPIONATE

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

FDA U.S. Food and Drug Administration Department of Health and Human Services

CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**CLOBETASOL PROPIONATE**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• CREAM; TOPICAL:0.05%** **• GEL; TOPICAL:0.05%** **• OINTMENT; TOPICAL:0.05%** **• SOLUTION; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
CLOBETASOL PROPIONATE (ANDA # 074128)	OINTMENT; TOPICAL	0.05%	Prescription	ALPHARMA US PHARM
CLOBETASOL PROPIONATE (ANDA # 074139)	CREAM; TOPICAL	0.05%	Prescription	ALPHARMA US PHARM
CLOBETASOL PROPIONATE (ANDA # 074331)	SOLUTION; TOPICAL	0.05%	Prescription	ALPHARMA US PHARM
CLOBETASOL PROPIONATE (ANDA # 075368)	GEL; TOPICAL	0.05%	Prescription	ALTANA
CLOBETASOL PROPIONATE (ANDA # 075391)	SOLUTION; TOPICAL	0.05%	Prescription	ALTANA
CLOBETASOL PROPIONATE (ANDA # 074087)	CREAM; TOPICAL	0.05%	Prescription	COPLEY PHARM
CLOBETASOL PROPIONATE (ANDA # 074089)	OINTMENT; TOPICAL	0.05%	Prescription	COPLEY PHARM
CLOBETASOL PROPIONATE (ANDA # 074392)	CREAM; TOPICAL	0.05%	Prescription	FOUGERA
CLOBETASOL PROPIONATE (ANDA # 074407)	OINTMENT; TOPICAL	0.05%	Prescription	FOUGERA
CLOBETASOL PROPIONATE (ANDA # 075205)	SOLUTION; TOPICAL	0.05%	Prescription	MORTON GROVE
CLOBETASOL PROPIONATE (ANDA # 075733)	CREAM; TOPICAL	0.05%	Prescription	STIEFEL
CLOBETASOL PROPIONATE (ANDA # 075338)	CREAM; TOPICAL	0.05%	Prescription	STIEFEL
CLOBETASOL PROPIONATE (ANDA # 075027)	GEL; TOPICAL	0.05%	Prescription	STIEFEL
CLOBETASOL PROPIONATE	OINTMENT;	0.05%	Prescription	STIEFEL

(ANDA # 075057)	TOPICAL			
CLOBETASOL PROPIONATE (ANDA # 074248)	OINTMENT; TOPICAL	0.05%	Prescription	TARO
CLOBETASOL PROPIONATE (ANDA # 074249)	CREAM; TOPICAL	0.05%	Prescription	TARO
CLOBETASOL PROPIONATE (ANDA # 075363)	SOLUTION; TOPICAL	0.05%	Prescription	TARO
CLOBETASOL PROPIONATE (ANDA # 075224)	SOLUTION; TOPICAL	0.05%	Prescription	TARO
CLOBETASOL PROPIONATE (ANDA # 075279)	GEL; TOPICAL	0.05%	Prescription	TARO

Back to Top | **Back to Previous Page** | **Start Over**

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

---

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**CLOBETASOL PROPIONATE (EMOLLIENT)**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• CREAM; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
CLOBETASOL PROPIONATE (EMOLLIENT) (ANDA # 075430)	CREAM; TOPICAL	0.05%	Prescription	ALTANA
CLOBETASOL PROPIONATE (EMOLLIENT) (ANDA # 075633)	CREAM; TOPICAL	0.05%	Prescription	TARO

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**CLOBEX**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• LOTION; TOPICAL:0.05%** **• SHAMPOO; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
CLOBEX (NDA # 021644)	SHAMPOO; TOPICAL	0.05%	Prescription	GALDERMA LABS
CLOBEX (NDA # 021535)	LOTION; TOPICAL	0.05%	Prescription	GALDERMA LABS LP

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration

Department of Health and Human Services

CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**CORMAX**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• CREAM; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
CORMAX (ANDA # 074220)	CREAM; TOPICAL	0.05%	Prescription	HEALTHPOINT

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**EMBELINE**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• GEL; TOPICAL:0.05%** **• OINTMENT; TOPICAL:0.05%** **• SOLUTION; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
EMBELINE (ANDA # 074222)	SOLUTION; TOPICAL	0.05%	Prescription	DPT
EMBELINE (ANDA # 076141)	GEL; TOPICAL	0.05%	Prescription	HEALTHPOINT
EMBELINE (ANDA # 074221)	OINTMENT; TOPICAL	0.05%	Prescription	HEALTHPOINT

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration

Department of Health and Human Services

CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**EMBELINE E**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• CREAM; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
EMBELINE E (ANDA # 075325)	CREAM; TOPICAL	0.05%	Prescription	HEALTHPOINT

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**OLUX FOAM**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• AEROSOL; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
OLUX FOAM (NDA # 021142)	AEROSOL; TOPICAL	0.05%	Prescription	CONNETICS

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**TEMOVATE**
Active Ingredient(s)	• CLOBETASOL PROPIONATE
Form(s) and Strength(s) Available	• CREAM; TOPICAL:0.05% • GEL; TOPICAL:0.05% • OINTMENT; TOPICAL:0.05% • SOLUTION; TOPICAL:0.05%

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
TEMOVATE (NDA # 019322)	CREAM; TOPICAL	0.05%	Prescription	GLAXOSMITHKLINE
TEMOVATE (NDA # 019323)	OINTMENT; TOPICAL	0.05%	Prescription	GLAXOSMITHKLINE
TEMOVATE (NDA # 019966)	SOLUTION; TOPICAL	0.05%	Prescription	GLAXOSMITHKLINE
TEMOVATE (NDA # 020337)	GEL; TOPICAL	0.05%	Prescription	GLAXOSMITHKLINE

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DRUG EVALUATION AND RESEARCH

Drugs@FDA

Overview

Drug Name	**TEMOVATE E**
Active Ingredient(s)	**• CLOBETASOL PROPIONATE**
Form(s) and Strength(s) Available	**• CREAM; TOPICAL:0.05%**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
TEMOVATE E (NDA # 020340)	CREAM; TOPICAL	0.05%	Prescription	GLAXOSMITHKLINE

Back to Top | Back to Previous Page | Start Over

Disclaimer

CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | Privacy | Accessibility | HHS Home Page

FDA/Center for Drug Evaluation and Research
Office of Training and Communications
Division of Library and Information Services
Update Frequency: Daily